Reviewer's report

Title: Polymorphisms in Multidrug Resistance 1, Cyclooxygenase-2 and Breast Cancer Resistance Protein Genes and Risk of Colorectal Cancer, a prospective population based case control study.

Version: 1 Date: 25 November 2008

Reviewer: jing shen

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Major Compulsory Revisions:

A prospective nested case control study was conducted to evaluate genetic variants in genes involved in the inflammation response and gut barrier pathways and colorectal cancer (CRC) risk. Potential interaction with lifestyle factors was also examined. The authors presented evidence to suggest that variations in the gut barrier pathway may play a role in the pathogenesis of CRC, but lack of association for inflammation response pathway. Interactions between NSAID use and genotype for MDR1 C3435T and COX-2 T8473C were observed.

Although the prospective study design should make the results potentially being powerful evidence for cancer risk estimation, some erroneous descriptions for the results lead to confusion in correctly distinguishing the role of studied SNPs. In a word, the major problem of this manuscript is the inconsistent for the results and the obtained conclusions. Such as, use of HRT (Table 1) was not more frequent among CRC cases (25, 16) than controls (31, 17) as described. The results showed in Table 5 are totally incorrectly described in the text (In the absence of NSAID use, there was no association between polymorphism and CRC risk, but among NSAID users, wild type allele carriers were at 2.34-fold (95% CI=1.22-4.48) higher risk of CRC than homozygous non-users). The OR of 2.34 is not the effect of wild type genotype, but the effect of NSAID because the reference is no NSAID user. How the author can get the conclusion that "whereas NSAID use was slightly protective among variant allele carriers”? In fact, the ORs were no statistically significant difference for wild type and variant allele of COX-2 T8473C (1.38 vs. 1.05). In fact, there is no heterogeneity by the status of this SNP.

Another problem is over-interpretation for the results. The associations observed in Table 3 were mostly non-significant and no clear trend, how to “indicating that a biologically effective polymorphism is probably in linkage disequilibrium with the two studied polymorphisms” (page 12). The incorrect in explaining the results and over-interpreting lead to mix up for the study conclusions. The author needs to rewrite the whole section of results and make it correctly and clearly. The discussion should also be changed according to the new description.

The reason for combining variant genotypes is not sufficient provided (page 12). Why all combination of genotypes is under a dominant model (Table 2 and 5)?
Do you have evidences?
The author need to explain and detailed discuss the finding that “Carriers of the variant allele of MDR1 C3435T were at lowered risk of CRC”, which is opposite to previous observation. The discussion should be more focus on CRC, not many other cancers. Strongly suggest using false positive report probabilities (FPRP) to estimate the possibility due to chance if the author thought they “cannot exclude that our positive findings are due to chance”.

Some important and basic genetic concepts are wrongly written according to the text, including “homozygous wild type carriers”, “wild type allele carriers” and “wildtype COX-2 GG-765-allele”.

Minor Essential Revisions
1) Please make the description for the study design consistent (“case control study” or “case-cohort study”).
2) Page 10, please indicate the reproducibility for the twenty sample;
3) Page 10 for statistical analysis section, if all models were adjusted for use of HRT, male who did not use HRT will be a missing data. Statistical power will be reduced sharply.
4) Page 11, please briefly introduce the process for interaction analysis. How the interaction P values are obtained in table 5?
5) Page 26, what is the meaning of p-value in table 2?
6) The reference group should be consistent in the whole text. TT as ref in table 3 and CC as ref in table 5. Check others.
7) No limitation for the current study has been clearly stated.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests.